UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/142,471	11/04/1998	STEFAN ROSE-JOHN	012627-009	2240

21839 7590 02/08/2005

BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 02/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/142,471	ROSE-JOHN, STEFAN	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-9,13 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-9 and 14* is/are rejected.

7)☒ Claim(s) *4, 5 and 13* is/are objected to.

8)☒ Claim(s) *1-5,7-9,13 and 14* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 November 1998* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on Nov. 22, 2004 has been entered.

Status of Claims

2. Claims 1-5, 7-9 13 and 14 are pending in the instant application. Claims 1-4 and 7-9 have been amended, claims 11 and 12 have been canceled and claims 13 and 14 have been added as requested by Applicant in the Paper filed Nov. 22, 2004.

All claims are currently under examination.

Withdrawn Objections and Rejections

3. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Sequence Compliance

4. Sequences are disclosed in Figures 1 and 2 without the required reference to the sequence identifiers (SEQ ID NOS:). The last amendment to the figures filed Oct. 28, 2002 (amendment E) has sequence identifiers for the signal peptide and the linker, but not for the fusion polypeptide H-IL-6 or the Sal1 sequence. Additionally, the Sal1 sequence appears not to be in the sequence listing, and so is required to be added.

The MPEP 2422 states:

"Nucleotide and/or Amino Acid Sequence Disclosures in Patent Applications
37 CFR 1.821. Nucleotide and/or amino acid sequence disclosures in patent applications.
(a) Nucleotide and /or amino acid sequences as used in § § 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides."

37 CFR 1.821(c) requires that each sequence disclosed in the application appear separately in the "Sequence Listing," with each sequence further being assigned a sequence identification number, referred to as "SEQ ID NO."

Applicant is given the statutory time from the mailing date of this communication within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Applicant needs to provide a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences recited in the claims and specification of the instant application which are encompassed by these rules, a substitute paper copy of that "Sequence

Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. §§ 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). **The instant specification will also need to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence.** For rules interpretation Applicant may call (703) 308-1123. See M.P.E.P. 2422.04.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5.1 Claims 1-3, 7-9 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a fusion protein of IL-6/IL-6R, CNTF/CNTFR or IL-11/IL-11R, does not reasonably provide enablement for any other fusion protein in the IL-6 family. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The instant specification on page 2 identifies cytokines in the IL-6 family as IL-6, IL-11, CNTF, OSM, LIF and CT-1. Claims previously rejected under 35 USC § 103 have been withdrawn, because Applicant has demonstrated that that the IL-6/IL-6R fusion protein has unexpected results, that the fusion protein has much higher activity than a complex of IL-6 and IL-6R, that is 100-1000 fold less of the fusion protein is required to produce the same results as the IL-6 and IL-6R complex (Fischer et al., Nature Biotechnology, Vol. 15, February 1997, pages 142-145, submitted by Applicant November 22, 2004). Fischer et al. also teach that in

contrast to other soluble cytokine receptors, the soluble forms of the receptors for IL-6, IL-11 and CNTF act agonistically upon binding, i.e., they can stimulate cells that on their own would not be able to respond to the cytokines (page 142, first column). Davis et al., Science, Vol. 259, March 1993, and Taga et al., Cell, Vol. 58, pages 573-581, 1989, teach, respectively, that the CNTF and IL-6 receptors are unusual in that the α receptor components constitute ligand binding domains that, in concert with their ligands, function effectively in soluble form as receptor agonists. Fischer et al. also teaches that it would be predicted that fusing other cytokines like CNTF or IL-11 to their respective soluble receptors might also result in proteins with greatly enhanced bioactivity (page 144, bottom paragraph). Therefore, the specification is enabling for making and using the fusion proteins IL-6/IL-6R, CNTF/CNTFR and IL-11/IL-11R. However, since the soluble receptors of LIF, OSM and CT-1 do not act agonistically, fusion proteins comprising these cytokines and their receptors would not be expected to have agonist activity or any specific activity. Therefore, the specification is enabling for fusion proteins of IL-6/IL-6R, CNTF/CNTFR and IL-11/IL-11R, but no others.

5.2 Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 14 encompasses pharmaceutical compositions comprising the claimed fusion polypeptide or DNA encoding the fusion polypeptide. Thus the claims encompass a "pharmaceutical use" for the compositions. For the claims to be enabled, the specification must teach how to use the composition for at least one pharmaceutical use without undue experimentation. Steadman's Medical Dictionary (24th Edition, 1982) defines "drug" as "a

therapeutic agent; any substance other than food, used in the prevention, diagnosis, alleviation, treatment or cure of disease in man and animal." Ansel et al (Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Edition), says "A drug is defined as an agent intended for use in the diagnosis, mitigation, treatment, cure or prevention of disease in humans or in other animals. One of the most astounding qualities of drugs is the diversity of their actions and effects on the body." The following are examples of "pharmaceutical uses": administering vitamin supplements (preventing disease); using labeled antibodies for in vivo imaging (diagnosing disease); administering a substance to alleviate a symptom of a disease (alleviating or treating disease); and administering an antibiotic (curing bacterial infection). Administering a polypeptide to produce antibodies to protect the individual from contracting a disease, i.e., vaccination, is a pharmaceutical use, however, administering a polypeptide to produce antibodies which are then collected from the animal and used in various ways is not a pharmaceutical use.

In the present situation, to enable a pharmaceutical use for the fusion polypeptide or DNA encoding it requires the specification to teach how to use the substance, without undue experimentation, for the prevention, diagnosis, alleviation, treatment or cure of a disease in the animal to which the substance is administered. However, the specification does not provide adequate guidance as to how the fusion polypeptides or DNA can be used to treat or diagnose any disorders. The specification on pages 9-11 demonstrates that fusion protein H-IL-6 stimulates haptoglobin expression in three human hepatoma cell lines, and that human $CD34^+$ cells treated with SCF, IL-3 and H-IL-6 were capable of forming about three times more colonies than cells treated with SCF, IL-3 and IL-6. The specification on pages 5-6 states:

"Furthermore, the present invention is suited for the ex vivo expansion of stem cells, particularly human stem cells. In this connection, it is especially remarkable that it is possible by means of a conjugate H-IL-6 according to the invention to obtain more stem cell colonies in the soft agar than possible with the individual components IL-6 and sIL-6R. Thus, the present invention also represents an important contribution to the well-calculated influence of blood cell formation. By means of a fusion polypeptide H-IL-6 which comprises the sequence of fig. 3 as IL-6 polypeptide, the present invention also provides a product which is suitable as IL-6 receptor antagonist. Such a product is of great therapeutic significance."

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

The MPEP states in section 2164.02:

"Lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art."

There are no examples of treatment by administration of the fusion polypeptide. It is not predictable from the *in vitro* experiments of the instant specification or from the teachings of the prior art that the fusion polypeptides could be used to treat any diseases or disorders.

In the instant case, an in vitro system of cell proliferation or haptoglobin expression is not predictive of treatment *in vivo*. Because of the complexity of biological systems, an *in vitro*

system is not sufficiently enabling for claims encompassing administration of the fusion protein. Undue experimentation would be required, and that is an invitation to experiment.

Additionally, claim 14 encompasses gene therapy, and the specification has not provided the support and guidance necessary to enable a method of gene therapy. The specification and prior art have not provided adequate guidance as to the vectors, promoters, transcriptional elements, and administration methods, for example, which are necessary for this type of therapy, and the specification does not provide any working examples. The level of skill in the art of gene therapy is low, and there have been very few successful gene therapy treatments. Thus, the specification fails to teach the skilled artisan how to use the claimed invention without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to perform gene therapy.

The state of the art of gene therapy at the time of the invention was low, with no unambiguous therapeutic benefits. Science News Report (Science 269, page 1050, column 2, paragraph 1, lines 6-15) states that while there have been reports of convincing gene transfer and expression, there is little evidence of a therapeutic result in patients or animal models. Anderson (Scientific American, September 1995, pages 124-128) states that *in situ* therapy, is hampered by effective ways for implanting corrected genes into various organs, as the genes are not expressed sufficiently to produce sufficient quantities of protein. Blau et al. (The New England Journal of Medicine, Nov. 2, 1995, pages 1204, column 1-2 bridging sentences and page 1205, column 1-2, bridging paragraph and page 1207, second column) wrote that expression and delivery of the gene desired for treatment were seen as the hurdles yet to be overcome, and that thus far clinical

trials have not shown convincingly that gene therapy is effective in treating disease in humans, and the field is still in its infancy.

Due to the lack of direction or guidance in the specification, the absence of working examples and teachings of the prior art, the unpredictability in the art, and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use a "pharmaceutical composition" comprising fusion polypeptides or DNA encoding fusion polypeptides. However, the specification enables the use of "a composition" comprising the fusion polypeptides or DNA encoding fusion polypeptides, and a pharmaceutically acceptable carrier. Deletion of the word "pharmaceutical" in the claims would therefore obviate the rejection.

Conclusion

6.1 Claims 1-3, 7-9 and 14 are rejected.

6.2 Claims 4, 5 and 13 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (571) 272-0829.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

Eileen B. O'Hara

EILEEN B. O'HARA
PATENT EXAMINER

Notice to Comply	Application No. 09/142,471	Applicant(s) Rose-John	
	Examiner Eileen B. O'Hara	Art Unit 1646	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Sal1 sequence not in sequence list or CRF, paper copy of sequence list incomplete.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY